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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1636	3

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

File 99

Office Action Summary	Application No. 09/139,425	Applicant(s) Esmon et al.
	Examiner WILLIAM SANDALS	Group Art Unit 1636

☒ Responsive to communication(s) filed on *Aug 25, 1998* .

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-25* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-25* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Information Disclosure Statement

1. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Drawings

2. This application has been filed with informal drawings which are acceptable for examination purposes only. Formal drawings will be required when the application is allowed.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-10 and 12-25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for cells in vitro, does not reasonably provide enablement for in vivo applications of the claimed invention. The specification does not enable any person skilled in

the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The claims are drawn to a method of (selectively) delivering molecules to a large vessel endothelial cell (nucleus) by binding a conjugate to an endothelial protein C receptor (EPCR). While applicants have shown the binding of a conjugate to an endothelial protein C receptor (EPCR) *in vitro*, they have not demonstrated any *in vivo* binding of a conjugate to an endothelial protein C receptor (EPCR). In order to do so, undue experimentation is required. Whether undue experimentation is needed is not based on a single factor, but rather a conclusion reached by weighing many factors. Many of these factors have been summarized in *In re Wands*, 858 F.2d 731, USPQ2d 1400 (Fed. Cir. 1988).

The Wands factors as they apply to the instant claimed invention are as follows:

a- The quantity of experimentation necessary to reduce the instant claimed invention to practice would involve binding of a conjugate to an endothelial protein C receptor (EPCR) *in vivo*.

b- Only prophetic guidance and no examples of binding a conjugate to an endothelial protein C receptor (EPCR) *in vivo* have been provided.

c- The nature of the invention is complex. The binding of molecules to EPC receptors has not been taught in the prior art, and use of ligands to deliver molecules to receptors on endothelial cells of large vessels is also not taught in the prior art.

d- Those of skill in the art have not taught how to use ligands of the EPCR to deliver molecules to the endothelial cells of large vessels, and teachings on how to make and use the invention must therefore be found in the instant specification. The failure to present such teachings constitutes a lack of enablement for the practice of the invention *in vivo*.

e- Therefore, given the analysis above, it must be considered that the skilled artisan would have needed to have practiced considerable non-routine, trial and error experimentation to enable the full scope of the claims.

5. Claims 5, 6 and 16-18 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to a method of (selectively) delivering genes to a large vessel endothelial cell (nucleus) by binding a conjugate to an endothelial protein C receptor (EPCR). While applicants have shown the binding of a conjugate to an endothelial protein C receptor (EPCR) *in vitro*, they have not demonstrated any *in vivo* delivering of a gene to an endothelial cell, which constitutes a method of gene therapy. In order to do so, undue experimentation is required. Whether undue experimentation is needed is not based on a single factor, but rather a conclusion reached by weighing many factors. Many of these factors have been summarized in *In re Wands*, 858 F.2d 731, USPQ2d 1400 (Fed. Cir. 1988).

The Wands factors as they apply to the instant claimed invention are as follows:

a- The quantity of experimentation necessary to reduce the instant claimed invention to practice would involve delivering a gene to an endothelial cell for gene therapy.

b- Only prophetic guidance and no examples of delivering a gene to an endothelial cell *in vivo* have been provided.

c- The nature of the invention is complex. Gene therapy is a new and developing art as recited in Marshall in the section titled "The trouble with vectors", and at page 1054, column 3, and at page 1055, column 3. The problems of gene delivery, gene targeting to reach the intended host cell, and then to reach the intracellular target are not yet solved, as taught in Verma et al. (see especially page 239, column 3, the box titled "What makes an ideal vector?" and page 242).

d- The prior art taught by Orkin et al. (see especially the section on "Gene transfer and expression" and "Gene therapy in man status of the field") described many problems in the developing field of gene therapy. Recited problems include: lack of efficacy, adverse short term effects and limited clinical experience, the inability to extrapolate experimental results and unreliability of animal models. Problems with the vector include: host immune response to the vector and the expressed product, difficulty of targeting the vector to the desired site, transient expression of the gene of interest and low efficiency of delivery of the vector to the targeted site.

e- The state of the art as taught by Verma et al., which states "the problems - such as the lack of efficient delivery systems, lack of sustained expression, and host immune reactions - remain formidable problems" and Anderson, W. F. (see page 25, top of column 1), which states

"[e]xcept for anecdotal reports of individual patients being helped, there is still no conclusive evidence that a gene-therapy protocol has been successful in the treatment of human disease".

f- Therefore, given the analysis above, it must be considered that the skilled artisan would have needed to have practiced considerable non-routine, trial and error experimentation to enable the full scope of the claims.

6. Claims 6 and 18 are rejected under 35 U.S.C. 112, first paragraph, as based on a disclosure which is not enabling. Teachings on the structure and location of action of ribozymes and antisense molecules are critical or essential to the practice of the invention, but not included in the claim(s) is not enabled by the disclosure. See *In re Mayhew*, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976).

The claims are drawn to an antisense oligonucleotide or ribozyme.

Antisense molecules have been shown to have biological activity in specific circumstances as taught by Rojanasakul, Y. (see especially the abstract, and pages 118-119 and 126). Rojanasakul states that antisense oligonucleotides can be easily degraded by the biological milieu, they are poorly taken up by the cells of the body, there are uncertainties with regard to cellular targeting, there is potential toxicity and problems of affinity to the target sites of antisense oligonucleotides exist. Successful making and using of antisense oligonucleotides for pharmaceutical purposes have been demonstrated in only a few reports, and there is no art recognized consensus between the isolated limited successes with antisense oligonucleotides for

pharmaceutical purposes as to how to make and use antisense oligonucleotides for pharmaceutical purposes.

The article from Nature Biotechnology, Vol. 15, entitled "Antisense '97: A roundtable on the state of the industry" states (see especially page 524) that the state of the art of use of antisense, and ribozymes is still poorly understood. Arthur Kreig States at page 522, column 1, "the percentage of accurate published antisense papers ranges from 50% of them being accurate to 5% being accurate - depending on who I talk to...reproducibility of findings has been a problem".

Since the use of antisense oligonucleotides for biological activity requires specific knowledge of exactly how to make and use the antisense oligonucleotide, this poses a high burden to provide specific information on how to make and use the antisense oligonucleotide. The instant claims and specification fail to provide the requisite specifics for making and using antisense oligonucleotides for pharmaceutical purposes as claimed. Therefore, applicants have not described the invention in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the invention was filed, had possession of the claimed invention.

7. Claims 13-25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for protein C, activated protein C, and antibodies to EPCR, does not reasonably provide enablement for any moiety which may bind to EPCR. The specification does

not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are drawn to a conjugate to an endothelial protein C receptor (EPCR). While applicants have shown the binding of a conjugate of protein C, activated protein C and antibody to an endothelial protein C receptor (EPCR) *in vitro*, they have not demonstrated any binding of any conjugate to an endothelial protein C receptor (EPCR). In order to do so, undue experimentation is required. Whether undue experimentation is needed is not based on a single factor, but rather a conclusion reached by weighing many factors. Many of these factors have been summarized in *In re Wands*, 858 F.2d 731, USPQ2d 1400 (Fed. Cir. 1988).

The Wands factors as they apply to the instant claimed invention are as follows:

a- The quantity of experimentation necessary to reduce the instant claimed invention to practice would involve binding of any conjugate to an endothelial protein C receptor (EPCR) *in vivo*.

b- Only prophetic guidance to binding of a conjugate of protein C, activated protein C and antibody to an endothelial protein C receptor (EPCR) *in vitro* have been shown and no examples of binding any other conjugate to an endothelial protein C receptor (EPCR) have been provided.

c- The nature of the invention is complex. The binding of molecules to EPC receptors has not been taught in the prior art, and use of ligands to deliver molecules to receptors on endothelial cells of large vessels is also not taught in the prior art.

d- Those of skill in the art have not taught how to use ligands of the EPCR to deliver molecules to the endothelial cells of large vessels, and teachings on how to make and use the invention must therefore be found in the instant specification. The failure to present such teachings constitutes a lack of enablement for the practice of the invention *in vivo*.

e- Therefore, given the analysis above, it must be considered that the skilled artisan would have needed to have practiced considerable non-routine, trial and error experimentation to enable the full scope of the claims.

8. Claims 1-12 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to a method of selectively delivering molecules to the nucleus of endothelium of the large vessels. While applicants have shown molecules which will bind to EPCR, which will subsequently be internalized into endothelial cells, and where some of the molecules are found in the nucleus, they have not demonstrated any selective method for delivering molecules to the nucleus using agents which bind to EPCR. In order to do so, undue experimentation is required. Whether undue experimentation is needed is not based on a single factor, but rather a conclusion reached by weighing many factors. Many of these factors have been summarized in *In re Wands*, 858 F.2d 731, USPQ2d 1400 (Fed. Cir. 1988).

The Wands factors as they apply to the instant claimed invention are as follows:

a- The quantity of experimentation necessary to reduce the instant claimed invention to practice would involve a clear demonstration that agents which bind to EPCR are selectively delivered to the nucleus of endothelial cells.

b- Guidance has been provided which demonstrates that agents which bind to EPCR are internalized into endothelial cells, and that some of the agent can be demonstrated to be found in the nucleus of the endothelial cells. However, no convincing evidence has been provided that the method is selective.

c- Examples have been provided which demonstrates that agents which bind to EPCR are internalized into endothelial cells, and that some of the agent can be demonstrated to be found in the nucleus of the endothelial cells. However, no convincing evidence has been provided that the method is selective.

d- The nature of the invention is complex. The delivery of molecules to the nucleus via EPCR has not been previously reported.

e- The prior art as taught by Rosenkranz et al. (see especially the abstract, the introduction and the discussion) show the introduction of molecules to the nucleus of a cell by binding an agent to a cell surface receptor. The process required the conjugation of poly-lysine to the agent and the molecule to be delivered to the nucleus.

f- The state of the art as taught by Jans et al. (see especially the summary, pages 404-405 and 409) describes the process of internalization and nuclear localization of agents bound to cell

surface receptors. The process requires a nuclear localization signal, and/or a secondary facilitator for entry of the agent into the nucleus.

g- The teachings of the instant specification on the localization of the EPCR to the nucleus is silent on the mechanism of action. There is a statement at page 8 of the instant specification that "no expression occurs if the construct is added to antibody that has not been modified with polylysine". Indicating that the nuclear localization of a gene to the nucleus did not occur in the absence of the polylysine as a facilitator of nuclear transport, as cited in Rosenkranz et al. above.

Evidence provided in the specification as to the experiments done to demonstrate nuclear localization in Examples 3, 4 and 5 at page 14, supported by Figures 1, 2 and 3 is missing the proper controls to demonstrate that the method was selective. The controls shown in Figure 1, do not include controls of a DNA-polylysine complex alone. Demonstration that the DNA was transported to the nucleus with an antibody-DNA-polylysine complex, without this critical control is unconvincing.

Since cell surface receptors are known to translocate to the nucleus in the process of activation, but that the process requires a nuclear localization signal and/or a secondary facilitator (such as polylysine conjugate). The mere demonstration of the localization of the EPCR to the nucleus is not found to be credible evidence that the process is "selective". Further proof is required to show that the presence of the agent bound to the EPCR is delivered by a selective process which is directly attributable to the instant invention.

Therefore, given the analysis above, it must be considered that the skilled artisan would have needed to have practiced considerable non-routine, trial and error experimentation to enable the full scope of the claims.

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 1, 5, 12, and 13-25 (and all dependent claims) are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

11. Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: The final recapitulation or correlation step which restates the preamble of the method.

12. Claims 5 and 17 recite the phrase "can be" which renders the claim(s) indefinite because the capacity of a compound to perform some function is merely a latent characteristic of said compound and said language carries no patentable weight. See MPEP § 2173.05(b), (d) and (g).

13. The term "or a fragment" in claim 14 is a relative term which renders the claim indefinite. The term "or a fragment" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably

apprised of the scope of the invention. Without proper guidance as to the metes and bounds of the claims, one of ordinary skill in the art would not know the characteristics of the antibody fragment in question.

14. Claims 13-25 are rejected as being indefinite. The claims are drawn to a conjugate of an agent which binds selectively to a EPCR and to a molecule to be delivered to a large vessel endothelial cell. No definition is provided for the agent which binds to an EPCR and no definition is provided for the molecule which binds to the agent. Without proper guidance as to the metes and bounds of the claims, one of ordinary skill in the art would not know the characteristics of the agent which binds selectively to a EPCR nor of the molecule to be delivered to a large vessel endothelial cell.

Claim Rejections - 35 USC § 102

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

16. Claims 13-15, 19, 20, 22, 24 and 25 are rejected under 35 U.S.C. 102(b) as being anticipated by Fukudome et al. (WO9605303).

The claims are drawn to a conjugate of an agent binding selectively to an endothelial protein C receptor (EPCR) and a molecule to be delivered to a large vessel endothelial cell. The

agent may be protein C, activated protein C or an antibody (which may be chimeric). The molecule to be delivered may be a protein, a drug or a diagnostic agent. There may be a coupling means which binds the agent and the molecule to be delivered, which may be a positively charged polymer or biotin-streptavidin.

Fukudome et al. (WO9605303) taught (see especially the abstract and pages 15-16, 18-26, the Figures and the Claims) a conjugate of an agent binding selectively to an endothelial protein C receptor (EPCR) and a molecule to be delivered to a large vessel endothelial cell. The agent may be protein C, activated protein C or an antibody (which may be chimeric). The molecule to be delivered may be a protein, a drug or a diagnostic agent. There may be a coupling means which binds the agent and the molecule to be delivered, which may be a positively charged polymer or biotin-streptavidin. Fukudome et al. (WO9605303) taught each and every aspect of the instant invention, thereby anticipating Applicant's invention.

17. (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

18. Claims 13-15, 19-20 and 22-25 are rejected under 35 U.S.C. 102(e) as being anticipated by US Pat No. 5,695,993 and US Pat No. 5,852,171.

The claims are drawn to a conjugate of an agent binding selectively to an endothelial protein C receptor (EPCR) and a molecule to be delivered to a large vessel endothelial cell. The agent may be protein C, activated protein C or an antibody (which may be chimeric). The

molecule to be delivered may be a protein, a drug or a diagnostic agent. There may be a coupling means which binds the agent and the molecule to be delivered, which may be a positively charged polymer or biotin-streptavidin.

US Pat No. 5,695,993 (see especially the abstract, the summary and columns 5-16) and US Pat No. 5,852,171 (see especially the abstract, the summary and columns 5-16) taught a conjugate of an agent binding selectively to an endothelial protein C receptor (EPCR) and a molecule to be delivered to a large vessel endothelial cell. The agent may be protein C, activated protein C or an antibody (which may be chimeric). The molecule to be delivered may be a protein, a drug or a diagnostic agent. There may be a coupling means which binds the agent and the molecule to be delivered, which may be a positively charged polymer or biotin-streptavidin. Fukudome et al. (WO9605303) taught each and every aspect of the instant invention, thereby anticipating Applicant's invention.

Claim Rejections - 35 USC § 103

19. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

20. Claims 16-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO96/05303, or US Pat No. 5,695,993 or 5,852,171 in view of Delporte et al. and Rosenkranz et al.

The claims are drawn to the conjugate described above and where the molecule to be delivered may be a nucleic acid molecule, which may be a cDNA, a gene, a triplex forming oligonucleotide, a ribozyme, a guide sequence for a ribozyme or an antisense.

WO96/05303, or US Pat No. 5,695,993 or 5,852,171 taught the invention as described previously. They did not teach that the molecule to be delivered may be a nucleic acid molecule, which may be a cDNA, a gene, a triplex forming oligonucleotide, a ribozyme, a guide sequence for a ribozyme or an antisense.

Rosenkranz et al. taught (see especially the abstract , the introduction, the Figures and the discussion) the delivery of a nucleic acid to a cell with a conjugate which binds to a cell surface receptor.

Delporte et al. taught (see especially the abstract, the introduction, the Figures and the introduction) the delivery of a nucleic acid to a cell with a conjugate which binds to a cell surface receptor.

It would have been obvious to one of skill in the art at the time of the instant invention to combine the teachings of WO96/05303, or US Pat No. 5,695,993 or 5,852,171 with Delporte et al. and Rosenkranz et al. to produce the instant claimed invention because WO96/05303, or US Pat No. 5,695,993 or 5,852,171 taught a conjugate of an agent binding selectively to an

endothelial protein C receptor (EPCR) and a molecule to be delivered to a large vessel endothelial cell where the agent was an antibody (which may be chimeric). Delporte et al. and Rosenkranz et al. taught a conjugate which binds to a cell surface receptor which facilitates the delivery of the conjugate to the cell. The delivery of conjugates to cells via a cell surface receptor is well known in the art, and the use of any receptor to bind a conjugate for delivery into a cell is an obvious choice within the purview of the ordinary skilled artisan. The instant claimed receptor, EPCR being one of many obvious receptors for the delivery of conjugates to a cell by way of a well known method of delivery as taught in WO96/05303, or US Pat No. 5,695,993 or 5,852,171 and Delporte et al. and Rosenkranz et al.

One of skill in the art would have been motivated at the time of the instant invention to combine the teachings of WO96/05303, or US Pat No. 5,695,993 or 5,852,171 with Delporte et al. and Rosenkranz et al. to produce the instant claimed invention because WO96/05303, or US Pat No. 5,695,993 or 5,852,171 taught a conjugate of an agent binding selectively to an endothelial protein C receptor (EPCR) and a molecule to be delivered to a large vessel endothelial cell where the agent was an antibody (which may be chimeric). Delporte et al. and Rosenkranz et al. taught a conjugate which binds to a cell surface receptor which facilitates the delivery of the conjugate to the cell. The delivery of conjugates to cells via a cell surface receptor is well known in the art as stated in Delporte et al. at page 524, top of column 1 "[t]hese complexes take advantage of receptor-mediated endocytosis", and the use of any receptor to bind a conjugate for delivery into a cell is an obvious choice within the purview of the ordinary skilled artisan. The

instant claimed receptor, EPCR being one of many obvious receptors for the delivery of conjugates to a cell by way of a well known method of delivery as taught in WO96/05303, or WO96/05303, or US Pat No. 5,695,993 or 5,852,171 with Delporte et al. and Rosenkranz et al. Further, a person of ordinary skill in the art would have had a reasonable expectation of success in the producing the instant claimed invention given the teachings of WO96/05303, or US Pat No. 5,695,993 or 5,852,171 with Delporte et al. and Rosenkranz et al.

21. Claim 21 is rejected under 35 U.S.C. 103(a) as being unpatentable over WO96/05303, or US Pat No. 5,695,993 or 5,852,171 in view of Rosenkranz et al. and Jans et al.

The claims are drawn to the conjugate described above and where the molecule to be delivered may be a transcription factor.

WO96/05303, or US Pat No. 5,695,993 or 5,852,171 taught the invention as described previously. They did not teach that the molecule to be delivered may be a transcription factor.

Rosenkranz et al. taught (see especially the abstract , the introduction, the Figures and the discussion) the general method of delivery of conjugate molecules to a cell via receptor-mediated endocytosis and nuclear transport.

Jans et al. taught (see the entire article) that the delivery of a molecule into a cell via receptor-mediated endocytosis is well known in the art, and transcription factors are taught to promote nuclear transport through nuclear localization signals within the transcription factors.

It would have been obvious to one of skill in the art at the time of the instant invention to combine the teachings of WO96/05303, or US Pat No. 5,695,993 or 5,852,171 with Rosenkranz et al. and Jans et al. to produce the instant claimed invention because WO96/05303, or US Pat No. 5,695,993 or 5,852,171 taught a conjugate of an agent binding selectively to an endothelial protein C receptor (EPCR) and a molecule to be delivered to a large vessel endothelial cell where the agent was an antibody (which may be chimeric). Jans et al. and Rosenkranz et al. taught a conjugate which binds to a cell surface receptor which facilitates the delivery of the conjugate to the cell. The delivery of conjugates to cells via a cell surface receptor is well known in the art, and the use of any receptor to bind a conjugate for delivery into a cell is an obvious choice within the purview of the ordinary skilled artisan. The instant claimed receptor, EPCR being one of many obvious receptors for the delivery of conjugates to a cell by way of a well known method of delivery as taught in WO96/05303, or US Pat No. 5,695,993 or 5,852,171 and Jans et al. and Rosenkranz et al.

One of skill in the art would have been motivated at the time of the instant invention to combine the teachings of WO96/05303, or US Pat No. 5,695,993 or 5,852,171 with Jans et al. and Rosenkranz et al. to produce the instant claimed invention because WO96/05303, or US Pat No. 5,695,993 or 5,852,171 taught a conjugate of an agent binding selectively to an endothelial protein C receptor (EPCR) and a molecule to be delivered to a large vessel endothelial cell where the agent was an antibody (which may be chimeric). Jans et al. and Rosenkranz et al. taught a conjugate which binds to a cell surface receptor which facilitates the delivery of the conjugate to

the cell. The delivery of conjugates to cells via a cell surface receptor is well known in the art as stated in Jans et al. at page 404, column 1 "endocytosis brings activated receptor molecules inside the cell, permitting their subsequent transport to specific intracellular compartments", and the use of any receptor to bind a conjugate for delivery into a cell is an obvious choice within the purview of the ordinary skilled artisan. The instant claimed receptor, EPCR being one of many obvious receptors for the delivery of conjugates to a cell by way of a well known method of delivery as taught in WO96/05303, or WO96/05303, or US Pat No. 5,695,993 or 5,852,171 with Jans et al. and Rosenkranz et al. Further, a person of ordinary skill in the art would have had a reasonable expectation of success in the producing the instant claimed invention given the teachings of WO96/05303, or US Pat No. 5,695,993 or 5,852,171 with Jans et al. and Rosenkranz et al.

Conclusion

22. Certain papers related to this application are ***welcomed*** to be submitted to Art Unit 1636 by facsimile transmission. The FAX numbers are (703) 308-4242 and 305-3014. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by the applicant or applicant's representative, and the FAX receipt from your FAX machine is proof of delivery. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications should be directed to Dr. William Sandals whose telephone number is (703) 305-1982. The examiner normally can be reached Monday through Friday from 8:30 AM to 5:00 PM, EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. George Elliott can be reached at (703) 308-4003.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group Receptionist, whose telephone number is (703) 308-0196.

William Sandals, Ph.D.

Examiner

May 10, 1999

NANCY DEGEN
PRIMARY EXAMINER